REMARKS

Claims 1-9, 11 and 13-20 are pending in the instant application. Form PTOL-326 and the Office Action indicating claim 12 to be pending is incorrect. Claim 12 was canceled in the amendment filed by Applicants on July 3, 2008. Accordingly, correction of the record is respectfully requested.

Claim 1 has been amended. Claim 2 has been canceled in light of the amendments to claim 1. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of the amendments and the following remarks.

Rejection of Claims under 35 U.S.C. 103(a)

The Examiner has rejected claims 1-9 and 11-20 under 35 U.S.C. 103(a) as being unpatentable over Modamio et al. (Int. J. Pharmaceutics 1998 173:141-148) in view of Hirano et al. (U.S. Patent 6,495,159) and Higo et al. (U.S. Patent 5,866,157) as further evidenced by Walters (Transdermal Drug Delivery, 1989, New York, NY, pp 97-246).

Applicants respectfully traverse this rejection.

At the outset, it is respectfully pointed out that claim 1 has been amended to be drawn to an adhesive patch

having a pressure-sensitive adhesive layer comprising bisoprolol and/or a pharmaceutically acceptable salt thereof, wherein said adhesive layer is a matrix type, and the composition thereof contains an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group, the acrylic polymer contains no alcoholic hydroxyl group in molecules, and the penetration rate of bisoprolol through skin is 3-300 $\mu g/h \cdot cm^2$.

The Examiner acknowledges at page 3 of the Office Action that the primary reference of Modamio does not teach a patch that possesses a matrix type adhesive layer, wherein the adhesive layer contains an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group such as that of 2-ethylhexylacrylate-butyl acrylate-acrylic acid copolymer. The Examiner further acknowledges that Modamio fails to teach the rate of penetration of bisoprolol through the skin as 4.0-300 $\mu g/h \cdot cm^2$ and absorption promoters as being for example, lauryl alcohol, an organic acid or isopropyl myristate.

Instead, the Examiner relies upon teachings in Hirano relating to a pressure-sensitive adhesive polymer layer that allows for controlled release of a medicine.

Reliance on teachings of Hirano, however, is improper.

MPEP 2143.01 and the case law are clear; if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

The invention of Hirano is "a percutaneous therapeutic apparatus which enables to control ooze of liquid medicine from a drug storage layer during preservation of the apparatus by laminating a pressure sensitive adhesive for controlling ooze of medicine to a drug releasing surface." See col. 1, lines 8-18 of U.S. Patent 6,495,159. At col. 2, lines 19-24, Hirano teaches that the "problems to be solved by this invention are to get rid of lowering of adhesion resulted from an interaction of an apparatus with medicine during preservation of the apparatus . . ." Further, at col. 7, lines 59-67, Hirano teaches that [S]ince the percutaneous therapeutic apparatus of this invention thus prepared has a structure in which the medicine is

encapsulated between the backing layer and the medicine releasing layer, it can accept any medicine having a wide range of viscosity from liquid-state medicine of low viscosity to that of high viscosity and it has the merit for preferable design of the safety, stability and effectiveness because it has a wide range of selection of the composition of medicine compared with a tape-medicine and so forth." Accordingly, clear from teachings of Hirano is that the intended purpose of the invention is to store medicine in a layer separate from the adhesive layer to get rid of lowering of adhesion resulting from the interaction of an apparatus with medicine during preservation of the apparatus. To modify the adhesive layer of Hirano to comprise the drug bisoprolol during preservation would clearly render the invention of Hirano unsatisfactory for its intended purpose. Thus in accordance with MPEP 2143.01, there is no suggestion or motivation to make the proposed modification of an adhesive layer of Hirano further comprising the drug bisoprolol as set forth in the instant claims.

Further, Hirano specifically distinguishes their invention from tape medicines, also know as matrix formulations. Any suggestion that it would be obvious to

use teachings of Hirano in a matrix formulation is thus contrary to its specific teachings.

Accordingly, it is improper to cite Hirano in the instant rejection.

Further, like Modamio, the other secondary references cited in this rejection, namely Higo et al. (U.S. Patent 5,866,157) and Walters (Transdermal Drug Delivery, 1989, New York, NY, pp 97-246) also provide no teaching or suggestion of an adhesive layer containing an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group, the acrylic polymer containing no alcoholic hydroxyl group in molecules.

Walters is merely cited as an illustration of typical absorption enhancers. This reference is silent with respect to an adhesive layer as claimed.

Higo teaches an adhesive layer for their matrix type patch formulation very different from the adhesive layer of the instant claimed invention. As acknowledged by the Examiner, in addition to a physiological substance and an absorption enhancer, the adhesive layer of Higo comprises an organic acid, a hydrophobic high molecular weight material, a tackifying resin, and a plasticizer. Exemplary organic acids are taught at col. 2, line 62 through col. 3, line 13

of Higo. Exemplary hydrophobic high molecular weight materials are taught at col. 3, line 64 through col. 4, line 9 of Higo. Exemplary tackifiers are taught at col. 4, lines 19-28. Exemplary plasticizers are taught at col. 4, lines 38-50. No where in these teachings of Higo is it taught or suggested to use an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group in the adhesive layer. Nor is it taught or suggested in Higo to use an acrylic polymer containing no alcoholic hydroxyl group in molecules. The only acrylic polymers taught by Higo are copolymers of at least two materials selected from the group comprising 2-ethylhexyl acrylate, vinyl acetate, methacrylate, methoxyacrylate and acrylic acid.

Thus, the combination of Modamio, Higo and Walter do not teach or suggest all claim limitations as required to render obvious the instant claimed invention.

Further, MPEP 2141 and *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007) state "[w]hen considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id* . at

___, 82 USPQ2d at 1396. While Modamio, Hirano, Higo and Walters may suggest means for improving the skin permeation rate of a drug, these references do not teach or suggest improvements in adhesive properties, crystal deposition and/or drug-content stability of matrix formulations. These are all problems to which the cited prior art is silent; these are all problems to be solved; and these problems are all solved by the instant claimed invention. Clearly, the instant claimed invention provides an improvement which is more than the predictable use of prior art elements according to their established functions taught in the cited prior art.

In addition, MPEP 2143.01 and *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) state "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. Since Modamio, Hirano, Higo and Walters do not teach or suggest improvements in adhesive properties, crystal deposition and/or drug-content stability of matrix formulations, the combination of these references is in no way predictive of the results obtained with the instant claimed invention.

Applicants respectfully direct the Examiner to Comparative Example 2 of the instant application which demonstrates that an adhesive patch comprising an adhesive layer containing 2-ethylhexylacrylate/vinyl acetate copolymer shows inferior adhesive properties and drug content stability as compared to a patch with an acrylic polymer obtained by copolymerizing a (meth)acrylic ester with a (meth)acrylic acid comprising a carboxyl group as claimed. Applicants further respectfully direct the Examiner to Example 4 of the instant application demonstrating that an adhesive patch comprising an adhesive layer containing 2-ethylhexyl acrylate/vinyl acetate/hydroxyethyl acrylate shows low drug-content stability compared to a patch with an acrylic polymer that contains no hydroxyl groups as claimed. Clear from these examples is that the instant claimed invention has unexpected effects which could in no way be predicted from the cited combination of references, none of which teach or suggest using an acrylic polymer with carboxyl group to prevent drug crystal deposition and to achieve sufficient adhesive properties in a matrix formulation and none of which teach or suggest using an acrylic polymer containing no hydroxyl group to obtain sufficient drug-content stability.

The instant claimed invention is thus clearly not obvious over the cited combination of references.

Withdrawal of this rejection is respectfully requested.

Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

/Kathleen A. Tyrrell/

Kathleen A. Tyrrell
Registration No. 38,350

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LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515